Attorney Docket # 4061-27PUS Patent

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Stanka PERC et al. Serial No.: 10/531,540 Filed: April 15, 2005 For: Pharmaceutical Formulation of Olanzapine	Examiner: Samira JM, Jean-Louis Group Art: 1627

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

SIR:

This is an appeal, pursuant to 37 C.F.R. § 41.37 from the decision of the Examiner in the above-identified application, as set forth in the Final Office Action wherein the Examiner finally rejected appellant's claims. The rejected claims are reproduced in the Appendix A attached hereto. A Notice of Appeal was filed on May 27, 2010.

The fee of $540 for filing an Appeal Brief (Large Entity) pursuant to 37 C.F.R. § 41.20 is submitted herewith. Any additional fees or charges in connection with this application may be charged to our Patent and Trademark Office Deposit Account No. 03-2412.

REAL PARTY IN INTEREST

The assignee, KRKA, Tovarna Zdravil, D.D., is the real party of interest in the above-identified U.S. Patent Application.

RELATED APPEALS AND INTERFERENCES

There are no other appeals and/or interferences related to the above-identified application at the present time.

STATUS OF CLAIMS

Claims 1-33 have been cancelled. Claims 34-51 have been rejected. Claims 34-51 are on appeal.

STATUS OF AMENDMENTS

There have been no Amendments filed subsequent to the Final Office Action.

SUMMARY OF THE CLAIMED SUBJECT MATTER

Claims 34-51 are on appeal in this application, with claim 34 being in independent form.

Specification citations are provided in accordance with 37 C.F.R. § 41.37. Citations are merely examples of where support may be found in the specification. There is no intention to suggest in any way that the terms of the claims are limited to the examples in the specification or the specific citations used. As demonstrated by the citations below, the claims are fully supported by the specification as required by law. However, it is improper to read limitations from the specification into the claims. The specification citations are not to be construed as claim limitations or in any way used to limit the scope of the claims. Neither the independent nor dependent claims contain "means plus function" nor "step plus function" language intended to invoke the provisions of 35 U.S.C. § 112, sixth paragraph, so no analysis of sections of the specification describing such means is needed.

Independent Claim 34

Claim 34 is the only independent and defines a pharmaceutical formulation (page 3, line 10 of the application as originally filed) comprising a **homogeneous** mixture (page 3, lines 17-30, page 4, lines 1-4 and 23-25 of the application as originally filed) of: (a) **uncoated** olanzapine or a pharmaceutically acceptable salt thereof as an active ingredient (page 3, lines 17-30 of the application as originally filed); (b) a monosaccharide and/or oligosaccharide and/or a reduced or oxidized form thereof (page 3, lines 9-12 of the application as originally filed); (c) a polysaccharide (page 3, lines 9-12 of the application as originally filed) and optionally; d) one or more additional excipients (page 3, lines 13-14 and page 7, lines 1-3 of the application as originally filed).

(Emphasis added.)

GROUNDS OF REJECTION TO BE REVIEWED IN APPEAL

1. Whether claims 34-51 are patentable under 35 U.S.C. §103(a) over Morris et al. (EP 0 830 858 A1) ("Morris") as evidenced by Nakajima et al. (U.S. 3,926,817) ("Nakajima")?

2. Whether claims 34-51 are patentable under 35 U.S.C. 103 over Chakrabarti et al. (U.S. 5,229,382) ("Chakrabarti") in view of Rubinstein et al. (Pharmaceutics: The Science of Dosage Form Design, 1988, Tablets, Chapter 18, pgs. 304-321) ("Rubinstein")?

ARGUMENT

I. Claims 34-51 are patentable under 35 U.S.C. § 103(a) over Morris as evidenced by Nakajima

Claims 34-51 stand rejected as being obvious under 35 U.S.C. §103(a) over Morris as evidenced by Nakajima. Appellants respectfully traverse.

1. Claims 34 and 36-48

Morris teaches an olanzapine formulation in which the active ingredient olanzapine is coated by a polymer. Morris repeatedly emphasizes the criticality of coating olanzapine with a suitable polymer in many paragraphs. *See*, for example, the abstract, page 2, lines 6-28 and 45-51, page 4, lines 45-57, and claim 1.

Morris does not disclose a formulation comprising uncoated olanzapine. Morris in fact contains many statements that would discourage or teach away a person of ordinary skill in the art from making an uncoated olanzapine formulation.

At page 2, lines 32-51, Morris discloses:

> Olanzapine, a potent compound showing promising activity for use in treating psychotic patients, tends to be metastable, undergo pharmaceutically undesired discoloration, and demands care to assure homogeniety of the finished solid formulation.
>
> Appellants have discovered that olanzapine undergoes undesirable discoloration when contacted with certain excipients including powder blends. Further, the discoloration is exacerbated by ambient air conditions, at elevated temperatures, and by moist environments.
>
> Although the discoloration phenomenon does not produce an increase in the number of total related substances, the browning and mottling appearance is not generally considered pharmaceutically acceptable for commercial purposes. Further, the discoloration is particularly disturbing when a tablet formulation is administered to a psychotic patient, which patient may be especially troubled by the changing appearance of their medication.
>
> The discoloration phenomenon is particularly troublesome for a granule formulation. Such formulation inherently exposes more olanzapine to ambient or humid conditions by virtue of the increased outer surface area relative to a solid tablet formulation. The present invention provides the desired pharmaceutically elegant granule formulation.
>
> Appellants have discovered that coating the olanzapine compound with a polymer selected from . . . as a coating or subcoating provides a uniform, physical stability and effectively prevents the undesired discoloration phenomenon in the formulation.

When reading the above disclosures, a person of ordinary skill in the art would not leave olanzapine uncoated, which would result in undesirable color change and appearance, in particular considering that the olanzapine formulation would be used for a patient suffering from hallucinations, delusions, and being out of touch with reality. See MPEP 1504.03 ("A *prima facie* case of obviousness can be rebutted if the applicant ...can show that the art in any material respect 'taught away' from the claimed invention...A reference may be said to teach away when a person of ordinary skill, upon reading the reference...would be led in a direction divergent from the path that was taken by the applicant." *In re Haruna*, 249 F.3d 1327, 58USPQ2d 1517 (Fed. Cir. 2001).

Nevertheless, the Examiner relies on a single sentence at col. 4, lines 47-49 of Morris to argue that a formulation comprising uncoated olanzapine as recited in the claims of the present application would have been obvious.

Specifically, at col. 4, lines 47-49, Morris discloses: "uncoated tablets stored at ambient conditions (approximately 23^0C and 40% relative humidity) in amber, high density polyethylene bottles do not show signs of discoloration after 24 months; however if the bottle is opened such that the tablets are exposed to open air ambient conditions then discoloration occurs **within** 5 days." (Emphasis added.) In view of the entire disclosure of Morris, it is clear that Morris includes this sentence to demonstrate the necessity of coating olanzapine. But the Examiner argues that this sentence suggests that tablets containing uncoated olanzapine "in fact **can be** made and is indeed within the purview of the skilled artisan." *See*, e.g., the Advisory Action dated May 11, 2010, page 2, first full paragraph, the final Office Action dated January 28, 2010, pages 2-3, bridging paragraph. The Examiner also concludes, "one of ordinary skill in the art

would have indeed found it obvious to formulate uncoated tablets of olanzapine if the intended use is for rapid consumption." *See* page 3,lines 8-9 the final Office Action. The Examiner's argument is flawed in several aspects.

First, as stated above, because Morris has clearly taught away from tablets containing uncoated olanzapine, a person of ordinary skill in the art would not select an uncoated tablet among other better choices (e.g., tablets comprising coated olanzapine), and modify it to arrive at the present invention, as suggested by the Examiner.

Second, the Examiner provides no evidence that there is a recognized use of olanzapine tablets for rapid consumption in the art. As disclosed in Morris, olanzapine is known for treating patients suffering psychotic conditions, such as hallucinations, delusions, and loss of touch with reality; and it is desired that an olanzapine product after being exposed to the air have long-term stability. That is why Morris proposes a pharmaceutically elegant solid oral formulation comprising olanzapine coated with certain polymers. *See*, e.g., the abstract, page 2, lines 14-18 and 35-51. Therefore, there is no basis for the Examiner's proposed modification of uncoated tablets of Morris for rapid consumption.

Third, Morris does not teach, suggest, or disclose a **homogenous mixture** of uncoated olanzapine as recited in the claims of the present application. It is the inventors of the present application that surprisingly found: "stable pharmaceutical formulations comprising olanzapine as the active ingredient, which do not show any undesired discoloration and have an excellent dose uniformity, can be prepared by a simple direct compression process if olanzapine or a pharmaceutically acceptable salt thereof is first homogenously mixed with certain excipients and then subjected to direct compression." *See* page 3, lines 23-26. Due to olanzapine's known

moisture sensitive, metastable nature in the art, a person of ordinary skill in the art would formulate olanzapine formulation very carefully, and try to develop a pharmaceutically elegant granule formulation. *See* Morris, page 2, lines 6-10, and Chakarabarti, col. 11, Example 4. Without knowing the surprising discovery by the present inventors, a person of ordinary skill in the art would not simply mix olanzapine with other excipients evenly to make a homogenous mixture, by e.g., direct compression.

At page 2, first paragraph of the Advisory Action, the Examiner argues, "It is incumbent upon applicant to demonstrate through side by side comparison that the prior art is not a homogenous mixture." But the Examiner fails to establish a *prima facie* case of obviousness in this regard. Therefore, the burden is not shifted to Appellants. In fact, even if Appellants want to demonstrate through "side by side comparison", Morris does not disclose a specific composition comprising uncoated olanzapine or method of making therefore for Appellants to compare with their own inventive composition. Nor does the Examiner identify a specific composition from Morris for Appellants to conduct the "side by side comparison." *See* MPEP 2142 ("The examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. If the examiner does not produce a *prima facie* case, the appellant is under no obligation to submit evidence of nonobviousness.")

Fourth, Morris does not clearly disclose a tablet composition comprising uncoated olanzapine. Although, as noted above, Morris mentions "uncoated tablets", it is not clear whether Morris refers to 1) tablets, none of which comprises a coating on the outmost surface of the final tablet product formed from the mixture of olanzapine, which may be coated or uncoated, and other excipients, or 2) tablets, each of which comprises uncoated olanzapine and

other excipients. Under the first interpretation, which is more consistent with the plain meaning of "uncoated tablets", then Morris does not disclose a composition comprising uncoated olanzapine as recited in claim 34.

Fifth, even if a person of ordinary skill in the art would intend to use an olanzapine product for rapid consumption, then this person would still not use the uncoated tablets of Morris. As stated above, according to Morris, when exposed to open air ambient conditions, the uncoated tablets discolor **within** 5 days. Therefore, a person of ordinary skill in the art would not formulate a composition comprising uncoated olanzapine, which according to Morris, may discolor any time, but by no later than 5 days, after exposure to the ambient conditions. The Examiner previously erroneously construed that the discolor only occurs by (i.e., not before) 5 days after the uncoated tablets are exposed to open air ambient conditions. *See* page 3, line 15 to page 4, line 2 of the final Office Action. After Appellants rebutted the Examiner's interpretation in this aspect, the Examiner remains silent in the Advisory Action.

Sixth, as explained in Appellants' previously submitted Amendment, if one would use uncoated olanzapine for rapid consumption, as suggested by the Examiner, s/he should at least warn physicians and patients that the uncoated olanzapine product should be consumed as soon as possible after the package is opened. In case that the package is opened and the product is not used up immediately, the unused product will have to be abandoned due to the occurrence of discoloring. Alternatively, one may consider placing only one unit dosage of tablet(s) in an amber, high density polyethylene bottle for one-time use, which will unduly increase the manufacturing cost and be unacceptable to a manufacturer. Also, because uncoated olanzapine is so sensitive to the open air, as taught in Morris, various precautions should be adopted to make

sure that the uncoated olanzapine formulation is packaged well and tight, therefore resulting in increased cost. In any case, the use of uncoated olanzapine, as proposed by the Examiner, is impractical. Therefore, in view of these problems and difficulties associated with uncoated olanzapine, as suggested by Morris, a person of ordinary skill in the art would not use any uncoated olanzapine for any use, even for rapid consumption, as suggested by the Examiner.

Moreover, as stated above, Morris taught that coated olanzapine tablets do not have any of the problems associated with uncoated olanzapine tablets, one would use coated olanzapine tablets for normal use or "rapid consumption" as proposed and speculated by the Examiner. *See* also MPEP 2145X. D.3 ("The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. *In re Hedges,* 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986).") In other words, if there is a better, more practical solution, without any particular reason, why would a person of ordinary skill in the art formulate an impractical olanzapine formulation and then package only one dosage of olanzapine formulation in one amber, high density polyethylene bottle for one time use?

In this aspect, MPEP2143 states:

> Note that combining known prior art elements is not sufficient to render the claimed invention obvious if the results would not have been predictable to one of ordinary skill in the art. *United States v. Adams*, 383 U.S. 39, 51-52, 148 USPQ 479, 483-84 (1966). In *Adams*, the claimed invention was to a battery with one magnesium electrode and one cuprous chloride electrode that could be stored dry and activated by the addition of plain water or salt water. Although magnesium and cuprous chloride were individually known battery components, the Court concluded that the claimed battery was nonobvious. The Court stated that "[d]espite the fact that each of the elements of the Adams battery was well known in the prior art, to combine them as did Adams required that a person reasonably skilled in the prior art must ignore" **the teaching away of the prior art that such batteries were impractical and that water-activated batteries were successful only when combined with electrolytes detrimental to the use of magnesium**

> **electrodes**. *Id.* at 42-43, 50-52, 148 USPQ at 480, 483. "When the prior art teaches away from combining certain known elements, discovery of successful means of combining them is more likely to be nonobvious."*KSR*, 550 U.S. at ___, 82 USPQ2d at 1395.

(Emphasis stated).

Seventh, the Examiner fails to properly evaluate the unexpected results of the present invention. *See* MPEP 2141 (Secondary considerations, such as unexpected results, must be evaluated under 35 U.S.C. § 103.) Although Appellants have presented this argument previously, the Examiner fails to consider it as required by MPEP2141.

Specifically, as noted above, according to the statement quoted by the Examiner from page 4, lines 45-48 of Morris, a person of ordinary skill in the art would expect that a formulation containing uncoated olanzapine would discolor any time but by not later than 5 days after the tablets are exposed to air under room temperature and 40% relative humidity. In contrast, it is Appellants, not others, who surprisingly discovered that a tablet formulation comprising a homogeneous mixture of uncoated olanzapine and other excipients in accordance with the present invention has good stability. As explained at page 3, last paragraph of the present application,

> It was surprisingly found by the present inventors that stable pharmaceutical formulations comprising olanzapine as the active ingredient, which do not show any undesired discoloration and have an excellent dose uniformity, can be prepared by a simple direct compression process if olanzapine or a pharmaceutically acceptable salt thereof is first homogeneously mixed with certain excipients and then subjected to direct compression. The direct compression is preferably performed in the absence of any solvent. In view of the fact that the excipients used by the present inventors are commonly used for manufacturing tablets, the finding that they allow the production of stable olanzapine formulations without any need for a coating or wet granulation was totally unexpected.

It is noted that at page 4, lines 3-10 of the final Office Action, the Examiner states: "no discoloration would occur since Morris explicitly teaches such formulations can in fact be formulated and that no discoloration occurs for 24 months." But the Examiner fails to mention that Morris explicitly states that its uncoated tablets when exposed to open air ambient conditions discolor within 5 days. **A person of ordinary skill in the art would by no means reasonably expect based on Morris the surprising discovery of the present invention before the filing of the present application.**

Eighth, the Examiner has previously stated that the findings by WIPO do not necessarily bind USPTO's examination of the counterpart application. While Appellants do not argue that USPTO should be necessarily bound by WIPO's decision, Appellants would like to again bring to the Examiner's attention the underlying substantive reasons for WIPO's findings that the claims of the corresponding PCT application are novel and have an inventive step in view of the same prior art applied by the Examiner here, i.e., Morris et al. For example, **WIPO's specific discussion** as to why the claims are novel and have an inventive step in view of Morris certainly **sheds light on how a person of ordinary skill in the art would understand Morris, the differences between Morris and the present invention, and whether the results of the present invention would be unexpected from Morris**. Indeed, WIPO's understanding about Morris is consistent with Appellants' above statement that Morris fails to teach a formulation comprising uncoated olanzapine and in fact teaches away from such a formulation.

Based on the foregoing, claim 34 is not obvious under 35 U.S.C. §103(a) over Morris as evidenced by Nakajima. For at least the same reasons, none of claims 36-48, each of which depends from claim 34, is obvious under 35 U.S.C. §103(a) over Morris and Nakajima.

2. Claim 35

Claim 35, which depends from claim 34, further recites that the formulation is prepared by a direct compression of the mixture into tablets in the absence of any solvent. Because claim 35 depends from claim 34, the reasons discussed above in connection with claim 34 also apply to claim 35.

Moreover, the Examiner fails to articulate any reason as to why the composition described in claim 35 would have been obvious. As noted above, although Morris mentions "uncoated tablets", it does not disclose, suggest, or teach how the uncoated tablets are prepared, let alone provides any reasonable expectation of success of preparing the uncoated tablets by direct compression.

Therefore, claim 35 is patentable under 35 U.S.C. §103(a) over Morris and Nakajima.

3. Claim 49

Claim 49, which depends from claim 34, further recites that the pharmaceutical formulation is in the form of an uncoated tablet. Because claim 49 depends from claim 34, the reasons discussed above in connection with claim 34 also apply to claim 49.

Moreover, the Examiner fails to articulate any reason as to why the composition described in claim 35 would have been obvious. As discussed above, because "uncoated tablets" and "uncoated olanapine" have different meanings, Morris at least fails to disclose one of these two features.

Therefore, claim 49 is patentable under 35 U.S.C. §103(a) over Morris and Nakajima.

4. Claim 50

Claim 50, which depends from claim 34, further recites that the active ingredient (a) is

distributed in a matrix formed by ingredients (b), (c), and (d). Because claim 50 depends from claim 34, the reasons discussed above in connection with claim 34 also apply to claim 50.

Moreover, the Examiner fails to articulate any reason as to why the composition described in claim 50 would have been obvious. As noted above, although Morris mentions "uncoated tablets", it does not disclose, suggest, or teach how the uncoated tablets are prepared, let alone a matrix composition.

Therefore, claim 50 is patentable under 35 U.S.C. §103(a) over Morris and Nakajima.

5. Claim 51

Claim 51, which depends from claim 34, further recites that formulation is in a tablet form, which does not have a layered structure. Because claim 51 depends from claim 34, the reasons discussed above in connection with claim 34 also apply to claim 51.

Moreover, the Examiner fails to articulate any reason as to why the composition described in claim 51 would have been obvious. As noted above, although Morris mentions "uncoated tablets", it does not disclose, suggest, or teach how the uncoated tablets are prepared, let alone the structure of the uncoated tablets.

Therefore, claim 51 is patentable under 35 U.S.C. §103(a) over Morris and Nakajima.

Based on the foregoing, reversal of the rejection of claims 34-51 under 35 U.S.C. §103(a) over Morris as evidenced by Nakajima is respectfully requested.

II. Claims 34-51 are patentable under 35 U.S.C. §103(a) over Chakrabarti in view of Rubinstein

Claims 34-51 stand rejected as being unpatentable over Chakrabarti in view of Rubinstein under 35 U.S.C. §103(a). Appellants respectfully traverse.

1. Claims 34 and 36-49

EP054436B1, the European counterpart to Chakrabarti (a U.S. patent), has been extensively discussed in the present application. *See* pages 1-2, the bridging paragraph and pages 2-3, the bridging paragraph of the application as originally filed.

As explained in Appellants' previously submitted Amendment, Chakrabarti fails to disclose a **homogeneous mixture** of: (a) uncoated olanzapine or a pharmaceutically acceptable salt thereof as an active ingredient; (b) a monosaccharide and/or oligosaccharide and/or a reduced or oxidized form thereof; (c) a polysaccharide and optionally; and d) one or more additional excipients, as recited in independent claim 34 of the present application. Chakrabarti merely teaches a formulation prepared by granulation and compression. *See* Example 4 of Chakrabarti.

Chakrabarti's method of granulating does not lead to a homogenous mixture of olanzapine with other excipients. As shown in Exhibit 1 (relevant pages of Remington's Pharmaceutical Sciences, 18th edition), granulation is used to form larger size of granules from powdered material, such as active ingredient and part of the excipients, and then the granules are blended and compressed together with lubricant, such as magnesium stearate to form tablets. Therefore, the tablets made by granulation are not a homogenous mixture, because the ingredients are not evenly distributed at different position or depth of the tablets. There are two types of granulation, i.e., dry granulation (with no solvent involved) and wet granulation (with solvent involved). Wet granulation is the most widely used and most general method of tablet preparation. *See*, Exhibit 1, page 1641, right column, 3rd paragraph. Dry granulation is used when tablet ingredients are sensitive to moisture or are unable to withstand elevated

temperatures. *See* Exhibit 1, page 1644, right column, 3rd full paragraph. Direct compression consists of compression tablets directly from powdered material without modifying the physical nature of the material itself.

Therefore, the tablet formulation made by granulation, as disclosed in Chakrabarti, is not a homogenous mixture.

The Examiner also argues that Chakarabarti discloses the use of conventional techniques for the preparation of olanzapine formulation and therefore discloses a homogenous mixture of olanzapine. *See* pages 4-5, bridging paragraph of the final Office Action and page 2, second paragraph of the Advisory Action. This argument lacks merit.

It is noted that at col. 8, lines 16-46, Chakrabarti broadly discloses that conventional techniques may be used to prepare a formulation, which can be in the form of tablets, capsules, injection solution, suspension, suppositories, and sachets. But nowhere does Chakarabarti disclose the use of direct compression or any other method to make a homogenous mixture. As stated above, wet granulation is the most widely used conventional technique, but it cannot produce a homogeneous mixture. Also as explained previously, due to olanzapine's known moisture sensitive, metastable nature in the art, a person of ordinary skill in the art would formulate olanzapine formulation very carefully, and try to develop a pharmaceutically elegant granule formulation, which is not a homogenous mixture. *See* Morris, page 2, lines 6-10, and Chakarabarti, col. 11, Example 4. Without knowing the surprising discovery by the present inventors, a person of ordinary skill in the art would not simply mix olanzapine with other excipients evenly to make a homogenous mixture by, e.g., direct compression.

The Examiner fails to identify which specific "conventional" technique a person of ordinary skill in the art would choose from among other "conventional" techniques to make a homogenous mixture. *See In re Mills*, 16 U.S. P.Q. 1430 (Fed. Cir. 1990); *In re Fritch*, 23 U.S.P.Q. 2d 1780 (Fed. Cir. 1992) (The mere fact that the prior art could be modified would not have made the modification obvious unless the prior art suggested the desirability of he modification.) Mere identification in the prior art of each element and characterizing it as "well-known" technology is insufficient to defeat the patentability of the combined subject matter as a whole. See, e.g., MPEP 2143.01; *In re Kahn*, 441 F.3d 977 (Fed. Cir. 2006) (Most inventions arise from a combination of old elements and each element may often be found in the prior art. However, mere identification in the prior art of each element is insufficient to defeat the patentability of the combined subject matter as a whole. Rather, to establish a *prima facie* case of obviousness based on a combination of elements disclosed in the prior art, the Board must articulate the basis on which it concludes that it would have been obvious to make the claimed invention. In practice, this requires that the Board explain the reasons one of ordinary skill in the art would have been motivated to select the references and to combine them to render the claimed invention obvious.)

Therefore, the Examiner's mere conclusion that the composition of the present invention would have been obvious through a "conventional" technique does not have merit. If the Examiner's approach were true, then virtually no invention would be patentable, because almost all of the inventions can be construed as being made through a "conventional technique" in the art.

The secondary reference Rubinstein discloses general methods of preparing compressed

tablets, and cannot remedy the deficiency discussed above in connection with the primary reference Chakrabarti et al. Therefore, combination of Chakrabarti and Rubinstein, as proposed by the Examiner, would not lead to the formulation of claim 34. Therefore, claim 34 is not obvious under 35 U.S.C. §103(a) over Chakrabarti et al. and Rubinstein.

Moreover, the unexpected results of the present invention as discussed above also show that claim 34 is not obvious under 35 U.S.C. §103(a) over Chakrabarti et al. and Rubinstein.

For at least the same reason, none of claims 36-49, each of which depends from claim 34, is obvious under 35 U.S.C. §103(a) over Chakrabarti and Rubinstein.

2. Claim 35

Claim 35, which depends from claim 34, further recites that the formulation is prepared by a direct compression of the mixture into tablets in the absence of any solvent. Because claim 35 depends from claim 34, the reasons discussed above in connection with claim 34 also apply to claim 35.

Moreover, the Examiner fails to articulate any reason as to why the composition described in claim 35 would have been obvious. Neither Chakrabarti nor Rubinstein discloses, suggests, or teaches preparation of an olanzapine formulation by direct compression of a mixture into tablets in the absence of any solvent.

Therefore, claim 35 is patentable under 35 U.S.C. §103(a) over Chakrabarti and Rubinstein.

3. Claim 50

Claim 50, which depends from claim 34, further recites that the active ingredient (a) is distributed in a matrix formed by ingredients (b), (c), and (d). Because claim 50 depends from

claim 34, the reasons discussed above in connection with claim 34 also apply to claim 50.

Moreover, the Examiner fails to articulate any reason as to why the composition described in claim 50 would have been obvious. Neither Chakrabarti nor Rubinstein discloses, suggests, or teaches a matrix composition.

Therefore, claim 50 is patentable under 35 U.S.C. §103(a) over Chakrabarti and Rubinstein.

5. Claim 51

Claim 51, which depends from claim 34, further recites that the formulation is in a tablet form, which does not have a layered structure. Because claim 51 depends from claim 34, the reasons discussed above in connection with claim 34 also apply to claim 51.

Moreover, the Examiner fails to articulate any reason as to why the composition described in claim 51 would have been obvious. Neither Chakrabarti nor Rubinstein discloses, suggests, or teaches an olanzapine formulation that is in a tablet form and does not have a layered structure.

Therefore, claim 51 is patentable under 35 U.S.C. §103(a) over Chakrabarti and Rubinstein.

Based on the foregoing, reversal of the rejection of claims 34-51 under 35 U.S.C. §103(a) over Chakrabarti and Rubinstein is respectfully requested.

CONCLUSION

For the foregoing reasons, it is respectfully submitted that appellant's claims are not rendered obvious and are, therefore, patentable over the art of record, and the Examiner's rejections should be reversed.

Respectfully submitted,
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CLAIMS APPENDIX

Listing of Claims:

34 A pharmaceutical formulation comprising a homogeneous mixture of: (a) uncoated olanzapine or a pharmaceutically acceptable salt thereof as an active ingredient; (b) a monosaccharide and/or oligosaccharide and/or a reduced or oxidized form thereof; (c) a polysaccharide and optionally; d) one or more additional excipients.

35. The pharmaceutical formulation of claim 34 wherein the formulation is prepared by a direct compression of the mixture into tablets in the absence of any solvent.

36. The pharmaceutical formulation of claim 34 comprising 40 to 80 weight % of the component (b).

37. The pharmaceutical formulation of claim 34 comprising 10 to 40 weight % of the polysaccharide.

38. The pharmaceutical formulation of claim 34 additionally comprising (d) up to 15 weight % of a disintegrant.

39. The pharmaceutical formulation claim 34 additionally comprising (e) *5* to 20 weight % of a binder.

40. The pharmaceutical formulation of claim 34 additionally comprising (f) 0.25 to 5 weight

% of a lubricant.

41. The pharmaceutical formulation of claim 34 additionally comprising (g) 0.1 to 0.5 weight % of a glidant.

42. The pharmaceutical formulation of claim 34, wherein the component (b) is selected from the group consisting of lactose, sucrose, dextrose, sorbitol, mannitol, lactitol, and mixtures thereof.

43. The pharmaceutical formulation of claim 42, wherein the component (b) is lactose.

44. The pharmaceutical formulation of claim 34, wherein the polysaccharide is selected from the group consisting of starch, cellulose, and mixtures thereof.

45. The pharmaceutical formulation of claim 44, wherein the polysaccharide is cellulose.

46. The pharmaceutical formulation of claim 34, wherein a mixture of 20 to 30 weight % of cellulose and 70 to 80 weight % of lactose is used as the components (b) and (c).

47. The pharmaceutical formulation of claim 46 comprising 70 to 90 weight % of a mixture of 20 to 30 weight % of cellulose and 70 to 80 weight % of lactose;

8 to 12 weight % of a binder;

3 to 10 weight % of a disintegrant;

0.3 to 2 weight % of a lubricant; and

0.2 to 0.4 weight % of a glidant.

48. The pharmaceutical formulation of claim 34 comprising olanzapine as the only pharmaceutically active ingredient.

49. The pharmaceutical formulation of claim 34 having the form of an uncoated tablet.

50. The pharmaceutical formulation of claim 34 wherein the active ingredient (a) is distributed in a matrix formed by ingredients (b), (c), and (d).

51. The pharmaceutical formulation of claim 34 wherein formulation is in a tablet form which does not have a layered structure.

EVIDENCE APPENDIX

Exhibit 1 of previously submitted Amendment dated March 29, 2010, copy of which is enclosed herewith.

RELATED PROCEEDINGS APPENDIX

None